Can family physicians have a role in eradication of hepatitis c infection?

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ABSTRACT

Background/Aims: Hepatitis C virus (HCV) infection is an important global public health problem. Application of screening programs is important for elimination of HCV in addition to direct-acting antiviral (DAA) therapies. In this study, we aimed to measure knowledge, attitudes, and behaviors of family physicians (FPs) who are important in screening programs regarding diagnosis, natural history, and treatment of HCV infection.

Materials and Methods: This study was designed as a cross-sectional study, aiming at measuring HCV knowledge levels about screening, diagnosis, natural history, and treatment of FPs working nationwide in Turkey, through a survey.

Results: The most common reason for the participants to perform anti-HCV test is the mandatory screening program before marriage by 70.9% (420). Of the participants included in the study, 29.6% (n=175) encountered anti-HCV test positivity at least once within the last 1 year. Of the physicians who encountered anti-HCV test positivity, 15.4% (n=27) had no knowledge about whether the patients went to a higher level center for further diagnosis, whereas 58.9% (n=103) did not know stage of the disease. Of participants, 14.5% (86) responded as DAA and 34.8% (206) responded as interferon + ribavirin treatment for hepatitis C infection.

Conclusion: FPs have lack and gaps of knowledge regarding screening, natural history, and treatment of HCV infection. The results of this study show that HCV training plans for FPs should cover all aspects of the infection, and emphasize the necessity of guidelines-based screening recommendations.

Keywords: Hepatitis C virus infection, anti-HCV positivity, family physicians, DAA, screening

INTRODUCTION

Hepatitis C Virus (HCV) infection is an important global public health problem (1). Global prevalence of HCV is 1.6% (1.3%-2.1%) for all age group, and it has affected over 100,000,000 people (1). Chronic HCV infection can lead to cirrhosis, and hepatocellular cancer, and eventually accounts for a considerable mortality related to hepatic diseases worldwide (2). Most patients are unaware of HCV infection; liver damage, which progresses silently from beginning of the infection, may emerge as cirrhosis after 20-30 years in 10%-20% of the infected persons (2, 3). Screening programs are recommended to identify the individuals who are a part of silent epidemics (intravascular substance users, prisoners, homosexual persons) (4, 5). Family Physicians (FPs), who are gatekeepers of the health system, play an important role in the screening of persons infected by HCV (6, 7). In a review, FPs have been shown a lack of knowledge about natural history, follow-up, and treatment of HCV infection (8). FPs may contribute to the screening programs by following screening programs and detecting the patients identified by laboratory findings (7). In our country, in addition to screening of the risk groups, each person who considers marrying is asked anti-HCV serologic testing by FPs. However, FPs are not directly responsible for confirming this test and directing for the treatment. The process may fail before the persons infected with HCV reach a gastroenterologist or an Infectious Diseases and Clinical Microbiology specialist who can provide treatment.

Direct-acting antiviral agents (DAAs), which have been recently introduced in the treatment of HCV infection, have much higher treatment success rates, shorter treatment duration, and lower side-effect profile (1). Recent publications have reported that HCV can be eliminated

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in the next 15 years if screening programs can be performed with success in addition to DAA therapies (1, 5). Ensuring effective participation in screening programs will be possible through knowing the basic knowledge of FPs about screening, clinical history, new treatments of HCV infection, and strengthening the missing points. In this study, we aimed to measure knowledge, attitudes, and behaviors of FPs regarding diagnosis, natural history, and treatment of HCV infection.

MATERIALS AND METHODS

Study type

This study was designed as a cross-sectional study, aiming at measuring HCV knowledge levels of FPs working nationwide in Turkey, through a survey. Family practice began in 2004 as a pilot application and was introduced in all provinces in 2013. Today, approximately 24,000 FPs cover nearly 100% of the country's population, over 80 million.

Determination of the sample

We used the following formula to calculate the minimum sample size to represent the target population:

$$Sample\ size = \frac{Z^2 \times p \times (1-p)}{c^2}$$

where

Z = Z value (e.g., 1.96 for 95% confidence level);
p = percentage picking a choice (prevalence), expressed as decimal;
c = margin of error, expressed as decimal.

Because there were no previously conducted studies in the region, to reach maximum number of samples, the p value was considered as 0.5, which is the assumption of 50% for our study. With 95% confidence level and 4% margin of error, minimum sample size was calculated as 600. The sample size was corrected using the following formula for the total number of FPs in Turkey (24,000).

$$n = \frac{N \times X}{X + N - 1}$$

where

n = Corrected sample size;
N = Total number of FPs (24,000);
X= Uncorrected sample size (600).

With the above formula, the corrected sample size was calculated as 586. The calculated sample was stratified and distributed to the geographic regions of the country based on density of FPs.

Data collection

Data were collected by answering the questions prepared on screening, natural history, and treatment of HCV infection, via the internet between January 11, 2018 and December 31, 2018. Web links were created for the survey and shared with the participant FPs after working hours in order to avoid knowledge exchanges when filling the survey in family health centers and to protect subjectivity. For distribution of the links among the provinces, a certain order was followed, and the link reached FPs who are members of Turkey Federation of Family Medicine. The participation was followed by one person in provinces via the web during the survey period. Data security was provided via the Surveymonkey Enterprise.

Variables

The first three questions of the survey involved demographic features (place of working, gender, number of years in the profession) of the FPs. Socioeconomic Development Index (SEDI) rankings of the provinces and regions are published at certain periods by the Turkish Ministry of Development (10). Patients in provinces with high SEDI scores represent individuals with better education and higher financial opportunities. In our country, treatment for HCV infection is delivered only in the university hospitals. Physicians' provinces of working were classified based on the facility of access to the HCV treatment and SEDI regions.

Participants were asked about the positive cases of the anti-HCV test they had encountered in the past year. They were asked why they wanted the test and they could mark multiple reasons. They were asked the meaning of positive cases of the anti-HCV test with emphasis on screening. They were asked to refer patients with positive test to a higher level center and knowing the stage of the disease and understanding the contribution to the power of attachment to care with yes/no questions. Sensitivity/specificity power of the test was asked in four options. Multiple choice questions were asked for the clinical course of hepatitis C infection and questions about whether there is a cure for the disease, treatment practice, and responses to treatment were presented as the only option. The choice of correct treatment of the disease was asked in multiple choice questions. Those who were able to make a meaningful combination of sofosbuvir, sofosbuvir 400

mg + Ledipasvir 90 mg, lamivudine, paritaprevir 75 mg + ritonavir 50 mg + ombitasvir 12.5 mg, dasabuvir 250 mg, entecavir, sofosbuvir 400 mg + velpatasvir 100 mg, oseltamivir, grazoprevir 100 mg + elbasvir 50 mg, daclatasvir 30 mg or 60 mg, simeprevir 150 mg, asunaprevir 100 mg, ribavirin 200 mg, and interferon group drug responses and those who did not mark the wrong medication were considered to respond correctly.

Statistical Analysis

Data were summarized as frequency (n) and percentage (%). Pearson's Chi-square test was used in the evaluation of the difference between categorical variables. Statistical analysis was performed by using the Statistical Packages for the Social Sciences (SPSS) version 20.0 (IBM Corp.; Armonk, NY, USA).

Participation was on voluntary basis. The approval for the study was received from the Kahramanmaras Sutcu Imam University Faculty of Medicine Ethic Committee, decision number 455, dated May 11, 2008.

RESULTS

At least 1000 physicians were reached in the study, and a total of 592 FPs from 75 provinces in Turkey participated in the study. The highest rate of participation was from Istanbul (19.3%; n=114), which is the largest city of Turkey, and from Marmara region (28.8%; n=165) with 30.7% of the total population of Turkey. The mean time since the graduation was 14.15±8.97 years, whereas this duration was found as 1-3 years in 16.4%, 3-10 years in 31.6%, and longer than 10 years in 52.6% of the participants. Of all participants, 66.6% (n=393) were male and 33.4% (n=199) were female. FPs' time since the graduation, presence of university hospital in their region of working, and evaluations according to the SEDI classification are presented in Table 1. The reasons of anti-HCV screenings within the last 1 year were asked with multiple choice questions; the most common cause was reported as marriage by 70.9% (n=420), routine screening request by 43.8 (n=259), preoperative screening by 19.3% (n=114), and postcoital test by 14.4% (n=85). Of the physicians included in our study, 29.6% (n=175) encountered anti-HCV test positivity at least once within the last 1 year. Of the physicians who encountered anti-HCV test positivity, 15.4% (n=27) had no knowledge about whether the patients went to a higher level center for further diagnosis, whereas 58.9% (n=103) did not know the stage of the disease. Of the FPs who encountered anti-HCV positivity within the last 1 year, 26.3% (n=46) had the knowledge that anti-HCV test alone is the diagnostic tool for HCV infection. Of the FPs encountered anti-HCV positivity, 55.4% (n=97) reported that it caused suspicion of infection. Behaviors of the FPs encountered anti-HCV positivity are shown in Figure 1. Of the FPs, 8.1% (n=10) encountered serologic positivity and thought that the disease is not progressive, and 20% (n=25) that the disease has no treatment. Of the FPs, 12.5% (n=74) reported that the test has a low sensitivity, and 29.6% (n=175) that the test has a high specificity.

Table 1. Demographic features of the participants.

	n	%
Gender		
Male	393	66.6
Female	199	33.4
SEDI in region of working		
1	183	30.91
2	63	10.64
3	57	9.63
4	52	8.78
5	101	17.06
6	136	22.97
Faculty which HCV patients can access to HCV treatment		
Yes	468	79
No	124	21
Time since the graduation		
1 -3 years	97	16.4
3-10 years	187	31.6
≥ 10 years	308	52

Of the participants, 7.1% (n=42) had knowledge that HCV infection does not become chronic. Regarding the treatment of HCV infection; 16.0% (n=95) of the participants reported that the disease has no treatment, 54.4% (n=322) that a high rate of treatment success could be achieved, 15.6% (n=92) that the disease could be treated, but the patients should be selected, and 14% (n=83) that the disease has treatment, but its treatment is not necessary. Of all participants, 20.8% (n=123) knew that successful response after the treatment is over 90%. Of the FPs who thought that the disease could be treated at a high rate, 35.7% (n=115) had knowledge that successful response after the treatment is over 90%. At the question about currently used drug options in the treatment of hepatitis C infection, 14.5% (n=86) reported DAA therapy, and 34.8% (n=206) interferon + ribavirin therapy. There was no statistically significant difference among times since the graduation in terms

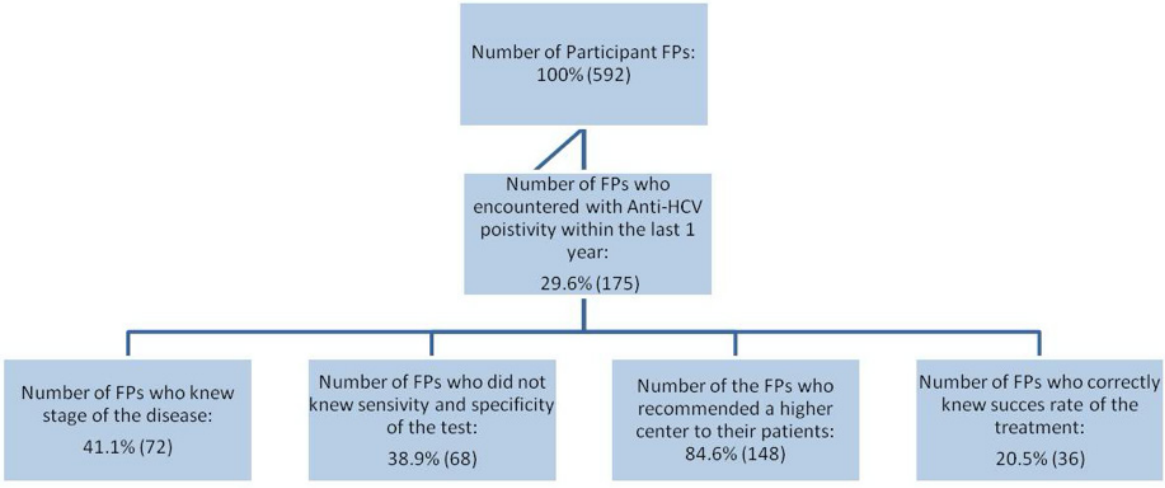

Figure 1. Family physicians' thoughts and behaviors about the disease, which have encountered antiHCV positivity for the last year.

Table 2. Evaluation of the knowledge about treatment of HCV according to the time since the graduation and region of working.

	Knowing that HCV may become chronic and progresses to cirrhosis and cancer		Not knowing that HCV has a treatment success rate over 90%		Knowing that HCV has a treatment success rate over 90%		Knowing DAA drugs		Knowing interferon group drugs		
	%	Number	%	Number	%	Number	%	Number	%	Number	p
n	100	n=499	100	n=469	100	n=123	100	n=86	100	n=201	
Time since the graduation:											
1-3 years	16.6	n=83	17.5	n=82	13.0	n=16	16.3	n=14	17.9	n=36	0.450
3-10 years	33.5	n=167	29.6	n=139	39.0	n=48	37.2	n=32	32.3	n=65	
≥ 10 years	49.9	n=249	52.9	n=249	48.0	n=49	46.5	n=40	49.8	n=100	
Faculty which HCV patients can access to HCV treatment:											
Yes	77.6	n=387	79.8	n=374	76.4	n=94	79.1	n=68	78.1	n=157	0.997
No	22.4	n=112	20.2	n=95	25.6	n=29	20.9	n=18	21.9	n=14	
SEDI in region of working:											
1	30.5	n=152	30.7	n=144	31.7	n=39	34.9	n=30	33.8	n=68	0.741
2	10.2	n=51	10.2	n=48	12.2	n=15	9.3	n=8	11.4	n=23	
3	9.6	n=48	9.4	n=44	10.6	n=13	5.8	n=5	8.0	n=16	
4	9.6	n=48	9.4	n=44	6.5	n=8	7.0	n=6	7.5	n=15	
5	16.2	n=81	17.9	n=84	13.8	n=17	16.3	n=14	13.4	n=27	
6	23.9	n=119	22.4	n=105	25.2	n=31	26.7	n=23	25.9	n=52	

of correct knowledge about treatment success of HCV infection (p=0.311), and knowledge about DAA therapies (p=0.450). There was also no significant difference in the SEDI of the region of working (p=0.741) and presence of a center that could treat HCV in the province of working (p=0.997). Correct answers of the FPs given to the options of natural history, rate of successful treatment, and treatment options according to time since the graduation, SEDI index of the region of working, and facility to treat HCV in the province of working are given in Table 2.

DISCUSSION

Studies conducted about the treatment of chronic HCV infection have led to great innovation within the last decade (3). In addition to more efficient treatments for elimination of HCV, high-risk groups should be determined, and awareness of effective screening, access to treatment, and protection should be maximized (11). Seroprevalence of HCV in Turkey is estimated as 1%, and majority of the patients do not know their diagnosis (12). There is no screening or surveillance program for HCV infection in Turkey (12). In action projection published by the Ministry of Health involving 2018-2023, education of FPs and providing them information about screening, directing, and treatment have been planned (13). FPs in Turkey are the gatekeepers of the health system, encompassing all society. FPs should have basic knowledge regarding diagnosis and management of HCV infection (14). In Turkey, 2.9% (2,327,904 persons) have received marriage report from FPs and have been screened for anti-HCV within the last 2 years (15). FPs have performed HCV screening most commonly before marriage with the rate of 70.9%. Considering other reasons for screening, FPs play an important role in finding treatable cases by screening 5 million individuals.

It is estimated that the number of newly diagnosed cases is about 5500, and the number of treated patients is approximately 4200 in our country (16). Recommendation by CDC to the first-line physicians for the diagnosis of HCV infection is based on determination of anti-HCV with enzyme immunoassay methods, and confirmation of the diagnosis with HCV RNA (17). Serologic determination of anti-HCV antibodies is the most commonly used screening method in Turkey, because this method is easy to use and inexpensive. Sample cut-off (S/Co) value determined sensitivity of anti-HCV testing. Public Health Institution of Turkey states that the samples obtained by FPs for screening work as S/Co value 1 in public laboratories have high sensitivity but low specificity (18). In our study, nearly half of the physicians reported low sensitivity and high sensitivity for the test. Lack of knowledge of the FPs about a test they perform was remarkable. In a study from Australia, 62% of practitioners reported that anti-HCV test positivity will cause suspicion of HCV (19). In this study also, physicians who encountered anti-HCV test positivity reported similar results.

FPs are found in a critical junction with their potential to identify persons with screening and refer to a physician who will treat them. Because there is still no vaccine developed against HCV, identification and treatment of the patients is important for protection and control. In a study from USA with FPs, 85% of 120 participants could properly order HCV RNA test, which is the next stage (20). In our country, FPs cannot order HCV RNA test, but they can direct the patient to a higher level center. In our study, 15.4% of the physicians who encountered anti-HCV test positivity have not referred their patients to a higher level center for further investigations. In CheCS study published in USA, 37.7% (3428) of 9086 anti-HCV positive patients identified had no HCV RNA test. Of the patients in this study, 32%-38% could receive clinical care, and about 13%-18% could receive treatment (21, 22). In the mentioned study, after persons were determined to have anti-HCV test positivity, breakdown and drop in the algorithm continues until the treatment. In a study from our country, 52.5% (n=83) of 158 patients determined to have anti-HCV test positivity had HCV RNA testing (23). One of the important reasons of the difference between our results and those in CheCS study published from USA might be that further tests and treatment are applied without charge because of general health insurance, which is applied in our country and covers every person. In our study, since the FPs have no sufficient knowledge about the disease, they cannot take the step to perform confirmatory test and to detect viremia.

In addition to the lack of information, the participants also have incorrect information; Most of them stated that there is no treatment for the disease and some of them stated that there is no progressive feature of the disease. In Turkey, this lack of information and misinformation of FPs seems to be the most important obstacle in front of the patient who can go to the specialist physician for free treatment. There are studies reporting that the clinical course information of hepatitis C infection is not sufficient in FPs.

Of the FPs, 58.9% (n=103) did not require questioning the stage of the disease in patients with positive screening test. In our study, 7.1% of the physicians had knowledge about that progressive disease does not become chronic. In a study from Australia, all participants knew that the disease progresses to cirrhosis (19). Of the FPs in our study, 16% thought that the disease has no treatment. More than one fourth of the physicians confirmed the knowledge that the disease has treatment; the patients were followed up without treatment or selected for the treatment. This confirmation suggests that the participants had not updated their knowledge since the period of interferon-based regimens. Another suggestive finding is that the participants thought interferon therapy more

than the others as the treatment of HCV infection. The physicians could not follow the current therapies. Physicians who checked the treatable option did not have accurate information about treatment success rates.

DAA agents approved in 2014 revolutionized the treatment of HCV infection. From the first approved three DAAs, there are regimens that have been shown to be pangenotypic and 100% successful (24). In our country, patients can benefit from the treatment free of charge. In a study by Falade-Nwulia et al. (20), 77% of FPs in the USA correctly knew DAA agents, and 67% were able to make combinations according to genotypes. One and perhaps most important of the main mechanisms causing this significant difference was that 59% of the FPs included in the study in the USA have been trained through online modules, conferences, and meetings related to HCV. Again, these physicians were working in primary health care centers that were affiliated an academic center. In our country, FPs kept themselves away from updated treatment of hepatitis C. Although it is not expected that FPs will treat patients with hepatitis C infection without consulting a specialist, knowing treatment options and risks/benefits of treatment is important (14). The lack of obligation to FPs in a screening or surveillance program on hepatitis C infection, and lack of in-service training may have been a major driver in this.

The weakness of this study was that screening methods based on guidelines were not addressed. It may be said that the physicians who completed the survey were more interested in hepatitis C, and their number was higher compared with FPs who did not participate in this study, and their responses reflect the "best level" in terms of knowledge. Our study is important in terms of being the first comprehensive study to measure knowledge of FPs about screening, natural history, and treatment of HCV infection.

In this study, we demonstrated FPs' lack and gaps of knowledge about screening, natural history, and treatment of HCV infection. If we aim to cure HCV infection, in addition to providing these drugs free of charge, closing this knowledge gap should be planned. This study sheds light on what can be emphasized in the trainings to be planned in order to eliminate lack of knowledge in FPs in order to provide strong cooperation in screening, which will give opportunity for treatment. The results of this study show that HCV training plans for FPs should cover all aspects of the infection, and emphasize the necessity of guideline-based screening recommendations.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Kahramanmaras Sutcu Imam University School of Medicine (Approval Date: 11.07.2018, Decision Number: 455/28).

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